AMENDMENT TO THE CLAIMS

The present document amends claims 5, 12, 25, 41, 46 and 49-51. According to 37 C.F.R. § 1.121(c), after entry of the present amendment, the status of the claims in the case is as follows:

Claims 1 and 2 Canceled

3. (Previously Presented) The method of claim 5, wherein said immunoconjugate binds to VEGF bound to the VEGF receptor VEGFR1 expressed by endothelial cells of the vasculature of said vascularized tumor.

4. (Previously Presented) The method of claim 5, wherein said immunoconjugate binds to VEGF bound within the stroma of said vascularized tumor.

5. (Currently Amended) A method for treating cancer, comprising administering to an animal that has a vascularized solid tumor, a metastatic tumor or metastases from a primary tumor, a therapeutically effective amount of:

(a) a first pharmaceutical composition comprising at least a first immunoconjugate that comprises at least a first ~~cleavage agent or~~ enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds to substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), wherein said enzyme is an enzyme set free by necrotic processes; thereby localizing said immunoconjugate to the vasculature or stroma of said vascularized solid tumor; and

(b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by ~~the cleavage agent or~~ said enzyme attached to said antibody in said first pharmaceutical composition, thereby releasing a substantially active drug specifically within the vasculature or stroma of said vascularized solid tumor.

6. (Original) The method of claim 5, wherein said at least a first antibody of said immunoconjugate is a monoclonal antibody or an antigen-binding fragment thereof.

7. (Original) The method of claim 5, wherein said at least a first antibody of said immunoconjugate is an scFv, Fv, Fab', Fab, diabody, linear antibody or $F(ab')_2$ antigen-binding fragment of an antibody.

8. (Original) The method of claim 5, wherein said at least a first antibody of said immunoconjugate is a human, humanized or part-human antibody or antigen-binding fragment thereof.

9. (Original) The method of claim 5, wherein said at least a first antibody of said immunoconjugate is a chimeric antibody or a recombinant antibody.

10. (Original) The method of claim 5, wherein said at least a first antibody of said immunoconjugate comprises at least a first variable region that includes an amino acid sequence region having the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:9.

11. (Original) The method of claim 5, wherein said at least a first antibody of said immunoconjugate is the monoclonal antibody 2C3 (ATCC PTA 1595).

12. (Currently Amended) The method of claim 5, wherein said immunoconjugate comprises said at least a first antibody operatively attached to two or more ~~cleavage agents or~~ of said enzymes.

Claims 13-24 Canceled

25. (Currently Amended) The method of claim 5, wherein said immunoconjugate comprises said at least a first antibody operatively attached to said at least a first ~~cleavage agent or~~ enzyme as a fusion protein prepared by expressing a recombinant vector that comprises, in the same reading frame, a DNA segment encoding said antibody operatively linked to a DNA segment encoding said ~~cleavage agent or~~ enzyme.

Claims 26-28 Canceled

29. (Previously Presented) The method of claim 5, wherein said first pharmaceutical composition is administered to said animal intravenously.

30. (Original) The method of claim 5, further comprising subjecting said animal to radiotherapy.

31. (Original) The method of claim 5, further comprising administering to said animal a therapeutically effective amount of at least a second anti-cancer agent.

Claims 32 and 33 Canceled

34. (Previously Presented) The method of claim 31, wherein said at least a second anti-cancer agent is a chemotherapeutic agent, radiotherapeutic agent, anti-angiogenic agent, apoptosis-inducing agent, steroid, antimetabolite, anthracycline, vinca alkaloid, antibiotic, cytokine, alkylating agent, coagulant or anti-tubulin drug or tumor-targeted form thereof.

35. (Previously Presented) The method of claim 34, wherein said at least a second anti-cancer agent is angiopoietin-2, endostatin, angiostatin, vasculostatin, canstatin, maspin, colchicine, taxol, vinblastine, vincristine, vindescine, a combretastatin, or tumor-targeted form thereof.

36. (Original) The method of claim 31, wherein said at least a second anti-cancer agent is a targeting agent-therapeutic agent construct comprising a therapeutic agent operatively linked to at least a first targeting region that binds to an accessible component of a tumor cell or tumor stroma or to a surface-expressed, surface-accessible, surface-localized, cytokine-inducible or coagulant-inducible component of tumor vasculature or intratumoral vasculature.

37. (Previously Presented) The method of claim 36, wherein said at least a first targeting region is operatively linked to a cytotoxic, cytostatic or anticellular agent, anti-angiogenic agent, apoptosis-inducing agent or anti-tubulin drug.

38. (Original) The method of claim 36, wherein said at least a first targeting region is operatively linked to Tissue Factor, truncated Tissue Factor or a Tissue Factor derivative or to an antibody, or antigen-binding fragment thereof, that binds to Tissue Factor, truncated Tissue Factor or a Tissue Factor derivative.

39. (Previously Presented) The method of claim 36, wherein said at least a first targeting region is operatively linked to a plant-, fungus- or bacteria-derived toxin.

Claim 40 Canceled

41. (Currently Amended) The method of claim ~~5~~ 49, wherein said at least a first cleavage agent or enzyme and said at least one substantially inactive prodrug are operably matched agents selected from the groups consisting of:

(a) alkaline phosphatase, arylsulfatase, serratia protease, thermolysin, subtilisin, a carboxypeptidase, a cathepsin, D-alanylcarboxypeptidase, β-galactosidase, neuraminidase, β-lactamase, penicillin amidase and cytosine deaminase; and

(b) a phosphate-containing prodrug, sulfate-containing prodrug, peptide-based prodrug, D-amino acid-modified prodrug, glycosylated prodrug, β-lactam-containing prodrug, optionally substituted phenoxyacetamide- or phenylacetamide-containing prodrug and 5-fluorocytosine.

42. (Original) The method of claim 5, wherein said animal is a human patient.

Claims 43-45 Canceled

46. (Currently Amended) A method for treating cancer, comprising administering to an animal that has a vascularized solid tumor:

(a) a first composition comprising at least a first immunoconjugate that comprises at least a first ~~cleavage agent or~~ enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that effectively competes with the monoclonal antibody 2C3 (ATCC PTA 1595) for binding to VEGF, wherein said enzyme is an enzyme set free by necrotic processes; thereby localizing said immunoconjugate to the vasculature or stroma of said vascularized solid tumor; and

(b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by ~~the cleavage agent or~~ said enzyme attached to said antibody in said first composition, thereby releasing a substantially active drug specifically within the vasculature or stroma of said vascularized solid tumor.

47. (Previously Presented) The method of claim 5, wherein said immunoconjugate localizes to the vasculature and stroma of said vascularized tumor.

48. (Previously Presented) The method of claim 5, wherein said at least a first antibody, or antigen-binding fragment thereof, of said immunoconjugate comprises at least a first variable region that includes an amino acid sequence region having the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:9.

49. (Currently Amended) A method for treating cancer, comprising administering to an animal that has a vascularized solid tumor, a metastatic tumor or metastases from a primary tumor, a therapeutically effective amount of:

(a) a first pharmaceutical composition comprising at least a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds to substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), thereby localizing said immunoconjugate to the vasculature ~~or stroma~~ of said vascularized solid tumor; ~~wherein said antibody, or antigen-binding fragment thereof, comprises at least a first variable region that includes an amino acid sequence region having the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:9;~~ and

(b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to said antibody in said first pharmaceutical composition, thereby releasing a substantially active drug specifically within the vasculature ~~or stroma~~ of said vascularized solid tumor.

50. (Currently Amended) A method for treating cancer, comprising administering to an animal that has a vascularized solid tumor, a metastatic tumor or metastases from a primary tumor, a therapeutically effective amount of:

(a) a first pharmaceutical composition comprising at least a first immunoconjugate that comprises at least a first ~~cleavage agent or~~ enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds

to substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), wherein said enzyme is an enzyme set free by necrotic processes; thereby localizing said immunoconjugate to the vasculature and stroma of said vascularized solid tumor; and

(b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by ~~the cleavage agent or~~ said enzyme attached to said antibody in said first pharmaceutical composition, thereby releasing a substantially active drug specifically within the vasculature and stroma of said vascularized solid tumor.

51. (Currently Amended) A method for treating cancer, comprising administering to an animal that has a vascularized solid tumor, a metastatic tumor or metastases from a primary tumor, a therapeutically effective amount of:

(a) a first pharmaceutical composition comprising at least a first immunoconjugate that comprises at least a first ~~cleavage agent or~~ enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds to substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595); wherein said enzyme is an enzyme set free by necrotic processes; and wherein said immunoconjugate binds to VEGF bound to the VEGF receptor VEGFR1 expressed by endothelial cells of the vasculature of said vascularized tumor, thereby localizing said immunoconjugate to the tumor vasculature; and

(b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by ~~the cleavage agent or~~ said enzyme attached to said antibody in said first pharmaceutical composition, thereby releasing a substantially active drug specifically within the vasculature of said vascularized solid tumor.

RESPONSE

I. Status of the Claims

Prior to the Action, claims 3-12, 25, 29-31, 34-39, 41, 42 and 46-51 were pending, of which the Office holds claims 36-39 to be drawn to initially non-elected species (see Applicants' first response at Section IV). Presently, claims 5, 12, 25, 41, 46 and 49-51 have been amended without prejudice or disclaimer. No claims have been cancelled or added.

Claims 3-12, 25, 29-31, 34-39, 41, 42 and 46-51 are therefore pending in the case. According to 37 C.F.R. § 1.121(c), a copy of the pending claims is provided in the amendment section.

II. Support for the Claims

Support for the revised claims exists throughout the specification and claims of the original and parent applications as filed, as well as in the current claims.

Independent claim 5 has been revised to replace "cleavage agent or enzyme" with "enzyme", which enzyme is further defined as "an enzyme set free by necrotic processes". As noted in the second Action at page 3, this is supported by the present and parent applications. For example, by the present specification at least at page 181, line 31 to page 182, line 5; and by priority application Serial No. 60/131,432, filed April 28, 1999 ("the '432 application"; Attorney Docket No. 3999.002590) at pages 118-119, particularly at page 119, lines 14-20. See also, '432 application at page 35, lines 8-17, page 113, lines 4-9 and page 157, lines 17-18.

Dependent claims 12 and 25 have been revised to accord with the wording of claim 5, and are supported thereby.

Claim 41 has been revised to depend from claim 49.

Independent claims 46, 50 and 51 have each been revised in the same manner as claim 5, and are supported by the present and parent applications as set forth above.

Claim 49 has been revised to remove the language referring to the amino acid sequences of SEQ ID NO:7 or SEQ ID NO:9; and to delete localization and drug release in the stroma, thus reciting only the vasculature.

It will therefore be understood that no new matter is included in the new claims.

III. Priority

The second Action at page 2 begins by according the present application "a priority date of April 28, 1998". Applicants believe that the present application has a priority date of April 28, 1999[1].

Applicants maintain that the present application has a priority date of April 28, 1999 as set forth in their first response, which is incorporated herein by reference.

Nonetheless, Applicants very much appreciate that the second Action has set forth language that the Office agrees to have priority to the '432 application, filed April 28, 1999, namely "antibodies administered in conjunction with prodrugs that are cleaved by enzymes set free by necrotic processes" (second Action at page 3, two instances). Accordingly, and without acquiescing with the former denial of priority in any way, Applicants have elected to revise independent claim 5, and most other claims in the application, to recite this exact language, which the Office itself indicates to have priority to April 28, 1999.

Claims 49 and 41 are the only claims remaining in the case that do not now include the exact language that the Office indicates to have priority to April 28, 1999. Applicants maintain that the April 28, 1999 priority date also applies to claims 49 and 41, as set forth in their first response, which is incorporated herein by reference.

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[1]Indeed, particular language with priority to the '432 application, filed April 28, 1999, is set forth in the second Action at page 3. However, in the unlikely event that the Office wishes to revisit the priority date issue, any such revision of the April 28, 1998 priority date accorded by the second Action at page 2 would have to be made via a further non-final Action.